Patent Claims

1. An agent for inhibiting the release, maturation and replication of members of the Flaviviridae family - genera: Flavivirus, Pestivirus, Hepacivirus - characterized in that it comprises, as the active component, at least one proteasome inhibitor in a pharmaceutical preparation.

2. An agent as claimed in claim 1, characterized in that it is used for inhibiting the release, maturation and replication of hepatitis C virus (HCV) and for the treatment and prophylaxis of HCV-induced hepatitides, flavivirus-induced fever, hemorrhages, leukopenia, thrombocytopenia, diarrheal diseases and encephalitides and also pestivirus-induced diseases.

3. An agent as claimed in claim 1 or 2, characterized in that use is made, as proteasome inhibitors, of substances

3.1. which inhibit, regulate or otherwise affect the activities of the ubiquitin/proteasome pathway

3.2. which specifically affect the enzymic activities of the complete 26S proteasome complex, and

3.3. which specifically affect the enzymic activities of the free 20S, catalytically active, proteasome complex, which is not assembled with regulatory subunits.

4. An agent as claimed in claim 3, characterized in that use is made, as proteasome inhibitors, of substances which, as proteasome inhibitors, are taken up by higher eukaryotic cells and, after having been taken up into a cell, interact with the catalytic subunits of the proteasome, and, in connection with this, block all or some of the proteolytic activities of the proteasome, i.e. the trypsin, chymotrypsin and postglutamyl peptide-hydrolyzing activities, within the 26S or the 20S proteasome complex.

5. An agent as claimed in claim 3 and 4, characterized in that, in addition to proteasome inhibitors, the pharmaceutical preparations also comprise other agents which affect, regulate or inhibit the cellular ubiquitin system, such as the activities
5.1. of the ubiquitin-conjugating enzymes and/or
5.2. of the ubiquitin-hydrolyzing enzymes.

6. An agent as claimed in claims 1 to 5, characterized in that use is made, as proteasome inhibitors, of substances which are administered in various forms *in vivo*, i.e. orally, intravenously, intramuscularly, subcutaneously or in encapsulated form, with or without cell specificity-carrying changes, which, due to using a particular administration and/or dose regime, exhibit low cytotoxicity, which do not elicit any side effects, or only elicit insignificant side effects, and which exhibit a relatively high metabolic half life and a relatively low clearance rate in the body.

7. An agent as claimed in claims 1 to 6, characterized in that use is made, as proteasome inhibitors, of substances which
a) are isolated in natural form from microorganisms or other natural sources, or
b) are formed from natural substances as a result of chemical modifications, or
c) are prepared completely synthetically, or
d) are synthesized *in vivo* using gene therapy methods.

8. An agent as claimed in claim 7, characterized in that use is made, as proteasome inhibitors, of substances which belong to the following substance classes:
8.a) naturally occurring proteasome inhibitors:

- peptide derivatives which contain epoxyketone structures C-terminally
- β-lactone derivatives
- aclacinomycin A (also termed aclarubicin),
- lactacystin and its chemically modified variants, such as the cell membrane-penetrating variant "clastolactacystein β-lactone"

8.b) synthetically prepared proteasome inhibitors:

- modified peptide aldehydes, such as N-carbobenzoxy-L-leucinyl-L-leucinyl-L-leucinal (also designated MG132 or zLLL), its boric acid derivative MG232; N-carbobenzoxy-Leu-Leu-Nva-H (designated MG115; N-acetyl-L-leucinyl-L-leucinyl-L-norleucinal (designated LLnL) and N-carbobenzoxy-Ile-Glu(OBut)-Ala-Leu-H (also designated PSI);

8.c) peptides which carry an α,β-epoxy ketone structure C-terminally, and also vinylsulfones, such as

8.d)1. carbobenzoxy-L-leucinyl-L-leucinyl-L-leucinevinylsulfone, or

8.d)2. 4-hydroxy-5-iodo-3-nitrophenylacetyl-L-leucinyl-L-leucinyl-L-leucinevinylsulfone (NLVS)

8.d) glyoxylic acid or boric acid radicals, such as

8.d)1. pyrazyl-CONH(CHPhe)CONH(CHisobutyl)$B(OH)_2$) and also

8.d)2. dipeptidyl boric acid derivatives, or

8.e) pinacol esters, such as benzyloxycarbonyl(Cbz)-Leu-Leu-boroLeu pinacol ester.

9. An agent as claimed in claim 7 and 8, characterized in that use is made, as particularly suitable proteasome inhibitors, of the epoxyketones

9.1. epoxomicin (epoxomycin, molecular formula: $C_{28}H_{86}N_4O_7$) and/or

9.2. eponemicin (eponemycin, molecular formula: $C_{20}H_{36}N_2O_5$).

10. An agent as claimed in claim 7 and 8, characterized in that use is made, as particularly suitable proteasome inhibitors from the PS series, of the compounds

10.1. PS-519 as β-lactone, and also as lactacystin derivative the compound IR-[1S,4R,5S]]-1-(1-hydroxy-2-methylpropyl)-4-propyl-6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione - molecular formula $C_{12}H_{19}NO_4$ - and/or

10.2. PS-341 as peptidyl-boric acid derivative the compound N-pyrazinecarbonyl-L-phenylalanine-L-leucine-boric acid - molecular formula $C_{19}H_{25}BN_4O_4$ - and/or

10.3. PS-273 (morpholine-CONH-(CH-naphthyl)-CONH-(CH-isobutyl)-B(OH)2) and its enantiomer PS-293 and/or

10.4. the compound PS-296 (8-quinolylsulfonyl-CONH-(CH-naphthyl)-CONH(-CH-isobutyl)-$B(OH)_2$) and/or

10.5. PS-303 (NH_2(CH-naphthyl)-CONH-(CH-isobutyl)-$B(OH)_2$) and/or

10.6. PS-321 as (morpholine-CONH-(CH-naphthyl)-CONH-(CH-phenylalanine)-$B(OH)_2$); - and/or

10.7. PS-334 (CH_3-NH-(CH-naphthyl-CONH-(CH-isobutyl)-$B(OH)_2$) and/or

10.8. the compound PS-325 (2-quinol-CONH-(CH-*homo*-phenylalanine)-CONH-(CH-isobutyl)-$B(OH)_2$) and/or

10.9. PS-352 (phenylalanine-CH_2-CH_2-CONH-(CH-phenylalanine)-CONH-(CH-isobutyl)1-$B(OH)_2$) and/or

10.10. PS-383 (pyridyl-CONH-(CH*p*F-phenylalanine)-CONH-(CH-isobutyl)-$B(OH)_2$).

11. The use of proteasome inhibitors as claimed in claims 1 to 10 for inhibiting the entry/internalization process, the replication and the maturation and release of Flaviviridae.

12. The use of proteasome inhibitors as claimed in claim 11 for inhibiting late processes in the Flaviviridae life cycle.

13. The use as claimed in claim 11, characterized in that proteasome inhibitors to a large extent or completely prevent, by blocking, the production of infectious virions from Flaviviridae-infected cells.

14. The use as claimed in claim 11, characterized in that proteasome inhibitors bring about inhibition of the release of virions and also a virtually complete reduction in the infectivity of the virions which are released.

15. The use as claimed in claim 11, characterized in that proteasome inhibitors suppress virus replication and consequently the fresh infection of host cells and thus the spread of an infection in vivo, i.e. in the liver tissue of an infected patient in the case of hepatitis C virus.

16. The use of proteasome inhibitors as claimed in claim 11 for inhibiting the replication of Flaviviridae in accordance with the following mechanisms

a) blocking/reducing the release of new virions

b) blocking/reducing the infectivity of released virions

c) blocking/reducing the spread of infection in cultures of host cells

d) blocking/reducing the spread of infection in infected organs *in vivo*.

17. The use of proteasome inhibitors as claimed in claim 11 for suppressing flavivirus infections and pestivirus infections in humans and animals.

18. The use of proteasome inhibitors as claimed in claim 11 for inducing the death of hepatocarcinoma cells.

19. The use of proteasome inhibitors as claimed in claim 18 for suppressing and/or preventing the development of liver cell carcinomas.

20. The use of proteasome inhibitors as claimed in claim 18 and 19 for treating patients who have established liver cell carcinomas.

21. The use of proteasome inhibitors as claimed in claims 18 to 20 for treating/controlling/preventing

21.1. HCV-induced liver cirrhosis and/or
21.2. HCV-induced liver cell carcinomas
21.3. medicament-induced liver carcinomas
21.4. genetically determined liver carcinomas
21.5. environmentally determined liver carcinomas and/or
21.6. liver carcinomas which are determined by a combination of viral and nonviral factors.

22. The use of proteasome inhibitors as claimed in claims 18 to 21 for selectively eliminating liver carcinoma cells which develop as the result of an

22.1. HCV infection, or
22.2. a corresponding coinfection with HCV and hepatitis B virus (HBV), or
22.3. a hepatitis delta virus (HDV)/HBV/HCV coinfection
22.4. human immunodeficiency virus (HIV)/HCV coninfections, or
22.5. HCV and coinfections with other viruses, bacteria or parasites.

23. The use of proteasome inhibitors as claimed in claims 18 to 22 for preventing the development, growth and metastasis of liver cell tumors and for

preferentially destroying liver carcinoma cells in HCV-infected patients.

24. The use of proteasome inhibitors as claimed in claim 11 for modulating the expression, modification and activity of the tumor suppressor protein p53 and other tumor suppressor proteins which are of importance in connection with hepatocellular carcinomas (HCCs).

25. The use of proteasome inhibitors as claimed in claim 11 for liver cell regeneration in patients suffering from hepatitis.

26. The use of proteasome inhibitors as claimed in claim 11 for regenerating patients following flavivirus infections.

27. The use of proteasome inhibitors as claimed in claim 11 for regenerating stabled animals following flavivirus or pestivirus infections.

28. The use of proteasome inhibitors as claimed in claim 11 for reducing the number of infected virus-producing cells in liver cell tissue.

29. The use as claimed in claim 11-14, characterized in that proteasome inhibitors alter the post-translational modification and proteolytic processing of Flaviviridae structural proteins and reduce the ability of the virus envelope proteins to dimerize and thereby reduce or block the release and infectivity of Flaviviridae.

30. The use of proteasome inhibitors as claimed in claim 11 for inhibiting both the maintenance and persistence of a previously established infection and of a secondary infection and consequently the spread of an infection, including blocking the spread of a Flaviviridae infection in vivo.

31. The use of proteasome inhibitors as claimed in claims 7 to 11 in combination with each other for the purpose of treating and controlling HCV-induced hepatitides, flavivirus-induced fever, hemorrhages and encephalitides and pestivirus-induced diseases.

32. The use as claimed in claim 31 in combination with therapeutic agents which are already used in the antiviral therapy of Flaviviridae infections.

33. The use as claimed in claims 31 and 32 for treating coinfections with different flaviviruses and pestiviruses.

34. The use as claimed in claims 31 and 32 for treating coinfections of HCV and immunodeficiency viruses HIV-1 and HIV-2.

35. The use as claimed in claim 34 for treating HCV/HIV coinfections in combination with HAART therapy.

36. The use of proteasome inhibitors as claimed in claim 11 for preventing a reinfection with HCV in connection with liver transplantations and other organ transplantations.

37. The use of proteasome inhibitors as claimed in claim 11 for preventing a reinfection with HCV in connection with cell therapies, by means of administering the agents before, during and after the transplantation.

38. The use of proteasome inhibitors as claimed in claim 11 for preventing a reinfection with HCV in connection with the transplantation of virus-free organs to chronic virus carriers who still possess residual virus and can infect new organs and also in connection with the transfer of virus-containing organs

from donors to virus-free patients.

39. The use of proteasome inhibitors as claimed in claim 11 for preventing the establishment of a systemic Flaviviridae infection immediately following contact with infectious virus.

40. The use of proteasome inhibitors as claimed in claim 11 for preventing a Flaviviridae infection in individuals who are at a high risk of fresh infection, such as doctors, at-risk personnel in establishments with high visitor traffic, drug addicts and travelers in regions which are highly endemic for Flaviviridae, and in patient treatment and for the members of families of chronic virus carriers.

41. The use of proteasome inhibitors as claimed in claim 11 for decreasing or eliminating a hepatitis by means of immune system-mediated mechanisms.

42. The use of proteasome inhibitors as claimed in claims 7 to 11 for producing agents and/or pharmaceutical preparations for inhibiting the release, maturation and replication of Flaviviridae.

43. The use of proteasome inhibitors as claimed in claim 42 for producing pharmaceuticals for the treatment and prophylaxis of HCV-induced hepatitides, flavivirus-induced fever, hemorrhages and encephalitides and pestivirus-induced diseases.